

## NATIONAL PBM COMMUNICATION *December 1, 2008*

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### ***Erlotinib (Tarceva®) and Important Safety Information in Patients with Hepatic Impairment***

Erlotinib (Tarceva®) prescribing information has been updated by OSI Pharmaceuticals, Inc. & Genentech, Inc. to include new safety information regarding use in patients with hepatic impairment in the WARNINGS section:

- “Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range.”<sup>1</sup>
- “TARCEVA dosing should be interrupted or discontinued if total bilirubin is greater than 3 x ULN and/or transaminases are greater than 5 x ULN in the setting of normal pretreatment values.”<sup>1</sup>
- Renal Failure, formerly under the PRECAUTIONS section, now appears under WARNINGS and includes the term “hepatorenal syndrome”.<sup>1</sup>

The DOSAGE AND ADMINISTRATION section of the product information also addresses dose interruption and/or discontinuation instructions as described in the WARNINGS section.<sup>1</sup>

These updated labeling changes resulted from the findings of a pharmacokinetic study where 15 patients receiving treatment with erlotinib died:

- 10 patients died during or within 30 days of the last dose;
  - 6 had baseline total bilirubin >3XULN.
- 8 patients died from progressive disease;
  - 1 died from hepatorenal syndrome;
  - 1 died from rapidly progressing liver failure.

This study evaluated patients with advanced solid tumors and moderate hepatic impairment (Child-Pugh criteria). All patients had advanced cancer affecting the liver (i.e., hepatocellular carcinoma, cholangiocarcinoma, or liver metastases).<sup>2</sup>

Cases of hepatic failure, hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported with erlotinib use.<sup>1</sup>

- 2 case reports describe patients with locally advanced pancreatic cancer who developed erlotinib-induced acute severe hepatitis that resolved upon discontinuation of Erlotinib.<sup>3,4</sup>
- 1 case report describes a patient with stage IV non-small cell lung cancer who developed Erlotinib –induced fulminant hepatic failure which resulted in death.<sup>5</sup>

#### References

1. Tarceva® [package insert]. Genentech, Inc. and OSI Pharmaceuticals, Inc.; South San Francisco, CA and Melville, NY.
2. FDA. [http://www.fda.gov/medwatch/safety/2008/tarceva\\_dhcp\\_letter.pdf](http://www.fda.gov/medwatch/safety/2008/tarceva_dhcp_letter.pdf) (Accessed September 24, 2008).
3. Ramanarayanan J, Scarpace SL. Acute drug-induced hepatitis due to Erlotinib. JOP2007; 8(1):39-43.
4. Saif MW. Erlotinib-induced acute hepatitis in a patient with pancreatic cancer. Clin Adv Hematol Oncol 2008;6:191-201.
5. Liu W, Makrauer FL, Qamar AA, Jaane PA, Odze RD. Fulminant hepatic failure secondary to Erlotinib. Clin Gastroenterol and Hepatology 2007;5:917-920.

#### **ACTIONS**

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS) and report completion of actions to the VISN Director.
- **Facility COS:** Forward this document to all appropriate providers who prescribe these medications (e.g., **oncology providers**, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate. Report completion of actions to the Facility Director.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).
- **VISN Directors:** Within 10 business days of receipt (due 12/15/2008), communicate to PBM/VAMedSAFE that all actions have been completed via the Feedback tool: [http://vaww.national.cmop.va.gov/PBM/visn\\_drug\\_recalls\\_alerts/default.aspx](http://vaww.national.cmop.va.gov/PBM/visn_drug_recalls_alerts/default.aspx).